

U.S. Patent No. 5,092,835 issued to Schurig et al. (describing the treatment of neurological disorders (such as autism), treatment of learning disabilities, and augmentation of mental and physical abilities of "normal" people by a combination of transcranial magnetic stimulation and peripheral electrical stimulation).

5 Independent studies have also demonstrated that TMS is able to produce a lasting change in neural activity within the cortex that occurs for a period of time after terminating the TMS treatment ("neuroplasticity"). For example, Ziemann et al., *Modulation of Plasticity in Human Motor Cortex after Forearm Ischemic Nerve Block*, 18 J Neuroscience 1115 (February 1998), disclose that TMS at subthreshold levels
10 (e.g., levels at which movement was not induced) in neuro-block models that mimic amputation was able to modify the lasting changes in neural activity that normally accompany amputation. Similarly, Pascual-Leone et al. (submitted for publication) disclose that applying TMS over the contralateral motor cortex in normal subjects who underwent immobilization of a hand in a cast for 5 days can prevent the decreased
15 motor cortex excitability normally associated with immobilization. Other researchers have proposed that the ability of TMS to produce desired changes in the cortex may someday be harnessed to enhance neuro-rehabilitation after a brain injury, such as stroke, but there are no published studies to date.

Other publications related to TMS include Cohen et al., *Studies of*
20 *Neuroplasticity With Transcranial Magnetic Stimulation*, 15 J. Clin. Neurophysiol. 305 (1998); Pascual-Leone et al., *Transcranial Magnetic Stimulation and Neuroplasticity*, 37 Neuropsychologia 207 (1999); Stefan et al., *Induction of Plasticity in the Human Motor Cortex by Paired Associative Stimulation*, 123 Brain 572 (2000); Sievner et al., *Lasting Cortical Activation after repetitive TMS of the Motor Cortex*, 54
25 Neurology 956 (Feb. 2000); Pascual-Leone et al., *Study and Modulation of Human Cortical Excitability With Transcranial Magnetic Stimulation*, 15 J. Clin. Neurophysiol. 333 (1998); and Boylan et al., *Magnetoelectric Brain Stimulation in the Assessment Of Brain Physiology And Pathophysiology*, 111 Clin. Neurophysiology 504 (2000).

Although TMS appears to be able to produce a change in the underlying cortex beyond the time of actual stimulation, TMS is not presently effective for treating many patients because the existing delivery systems are not practical for applying stimulation over an adequate period of time. TMS systems, for example, are relatively complex and require stimulation treatments to be performed by a healthcare professional in a hospital or physician's office. TMS systems also may not be reliable for longer-term therapies because it is difficult to (a) accurately localize the region of stimulation in a reproducible manner, and (b) hold the device in the correct position over the cranium for a long period, especially when a patient moves or during rehabilitation. Furthermore, current TMS systems generally do not sufficiently focus the electromagnetic energy on the desired region of the cortex for many applications. As such, the potential therapeutic benefit of TMS using existing equipment is relatively limited.

Direct and indirect electrical stimulation of the central nervous system has also been proposed to treat a variety of disorders and conditions. For example, U.S. Patent No. 5,938,688 issued to Schiff notes that the phenomenon of neuroplasticity may be harnessed and enhanced to treat cognitive disorders related to brain injuries caused by trauma or stroke. Schiff's implant is designed to increase the level of arousal of a comatose patient by stimulating deep brain centers involved in consciousness. To do this, Schiff's invention involves electrically stimulating at least a portion of the patient's intralaminar nuclei (*i.e.*, the deep brain) using, *e.g.*, an implantable multipolar electrode and either an implantable pulse generator or an external radiofrequency controlled pulse generator. Schiff's deep brain implant is highly invasive, however, and could involve serious complications for the patient.

Likewise, U.S. Patent No. 6,066,163 issued to John acknowledges the ability of the brain to overcome some of the results of an injury through neuroplasticity. John also cites a series of articles as evidence that direct electrical stimulation of the brain can reverse the effects of a traumatic injury or stroke on the level of consciousness. The system disclosed in John stimulates the patient and modifies the parameters of stimulation based upon the outcome of comparing the

patient's present state with a reference state in an effort to optimize the results. Like Schiff, however, the invention disclosed in John is directed to a highly invasive deep brain stimulation system.

Another device for stimulating a region of the brain is disclosed by King in U.S. Patent No. 5,713,922. King discloses a device for cortical surface stimulation having electrodes mounted on a paddle implanted under the skull of the patient. The electrodes are implanted on the surface of the brain in a fixed position. The electrodes in King accordingly cannot move to accommodate changes in the shape of the brain. King also discloses that the electrical pulses are generated by a pulse generator that is implanted in the patient remotely from the cranium (*e.g.*, subclavicular implantation). The pulse generator is not directly connected to the electrodes, but rather it is electrically coupled to the electrodes by a cable that extends from the remotely implanted pulse generator to the electrodes implanted in the cranium. The cable disclosed in King extends from the paddle, around the skull, and down the neck to the subclavicular location of the pulse generator.

King discloses implanting the electrodes in contact with the surface of the cortex to create paresthesia, which is a sensation of vibration or "buzzing" in a patient. More specifically, King discloses inducing paresthesia in large areas by applying electrical stimulation to a higher element of the central nervous system (*e.g.*, the cortex). As such, King discloses placing the electrodes against particular regions of the brain to induce the desired paresthesia. The purpose of creating paresthesia over a body region is to create a distracting stimulus that effectively reduces perception of pain in the body region. Thus, King appears to require stimulation above activation levels.

Although King discloses a device that stimulates a region on the cortical surface, this device is expected to have several drawbacks. First, it is expensive and time-consuming to implant the pulse generator and the cable in the patient. Second, it appears that the electrodes are held at a fixed elevation that does not compensate for anatomical changes in the shape of the brain relative to the skull, which makes it difficult to accurately apply an electrical stimulation to a desired target site of the